Nanoparticles in the ocular drug delivery

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Abstract

- Ocular drug transport barriers pose a challenge for drug delivery comprising the ocular surface epithelium, the tear film and internal barriers of the blood-aqueous and blood-retina barriers. Ocular drug delivery efficiency depends on the barriers and the clearance from the choroidal, conjunctival vessels and lymphatic. Traditional drug administration reduces the clinical efficacy especially for poor water soluble molecules and for the posterior segment of the eye. Nanoparticles (NPs) have been designed to overcome the barriers, increase the drug penetration at the target site and prolong the drug levels by few internals of drug administrations in lower doses without any toxicity compared to the conventional eye drops. With the aid of high specificity and multifunctionality, DNA NPs can be resulted in higher transfection efficiency for gene therapy. NPs could target at cornea, retina and choroid by surficial applications and intravitreal injection. This review is concerned with recent findings and applications of NPs drug delivery systems for the treatment of different eye diseases.

- KEYWORDS: nanoparticles; eye; drug delivery

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INTRODUCTION

Various efforts have been made to improve the bioavailability and the drug release and absorbing rate from formulations or dosage forms. Engineered nanodevices and nanostructures operate human biological systems at the single-cell and molecular level [1]. Nanoparticles (NPs) with size range from 10nm to 1 000nm improved topical passage of large, poorly water-soluble molecules through the barriers of ocular system [2]. Superficial barriers impede direct and systemic drug access to the specific site of action. Drug loaded NPs favorable biological properties include prolonging the residence time of eye drops and decreasing toxicity and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor minimizing precorneal drug loss by the rapid tear fluid turnover [3-4]. The techniques were planned to transform NPs from lipophilic to hydrophilic and downregulated irritant to the eye. Some methods loaded with NPs could be very useful for extended delivery of ophthalmic drugs [5-7]. NPs deliver ocular drugs to the target sites were applied in the treatments of many eye diseases as follows [1] (Figure 1).

GLAUCOMA

Glaucoma leads to vision loss even blindness. The progresses of drug delivery systems can lead to greater treatment options and preservation of vision in glaucoma [8]. New drugs were anticipated effective drug bioavailability and sustained time without toxic effects.

New Methods were Explored to Enhance the Drug Delivery Efficient and Patient Adherence

Drug delivery systems have the potential to improve patient adherence, reduce side effects, increase efficacy, and preserve sight for glaucoma patients [9]. Mucus-penetrating particle topical administration nanotechnology could improve the effectiveness of approaches for glaucoma [9]. Hybrid polyamidoamine (PAMAM) dendrimer hydrogel/poly (lactic-co-glycolic acid) (PLGA) nanoparticle platform (HDNP) for codelivery of two traditional antiglaucoma drugs brimonidine and timolol maleate showed no cytotoxic effect and prolonged residence time with slowly released period thus enhancing drug bioavailability in glaucoma treatments [10]. Brimonidine tartrate (BT) loaded chitosan (CS) NPs prepared by inducing the ionic gelation upon addition of sodium tripolyphosphate (TPP) could help to reduce dosage frequency by sustained drug release in the treatment of glaucoma [10]. Methazolamide, binding to CaP NPs prolong the intraocular pressure (IOP)-lowering effect duration time, has been shown to be useful in the local treatment of glaucoma [12]. Hyaluronic acid modified chitosan NPs (CS-HA-NPs) may be a promising carrier for glaucoma drug delivery [18]. Positively-charged pilocarpine HCl-loaded polymeric and lipid NPs by quasi-emulsion solvent evaporation technique was potent for glaucoma [14].
Some Traditional Antiglaucoma Administrations were Cooperated with Nanomedicine Approach to Improve Drug Bioavailability and Decrease Drug Dosage

Formulation of dorzolamide hydrochloride and Methazolamide- loaded solid lipid NPs (SLN) in a nanoemulsion form offers a more intensive treatment of glaucoma, a decrease in the number of applications per day, and a better patient compliance compared to conventional eye drops [4,19]. Eudragit NPs of brimonidine tartrate made by double emulsion-solvent evaporation technique prolong the drug release in vitro and prolong IOP reduction efficacy in vivo. This was potential for the treatment of open-angle glaucoma [18]. Nanovesicles were developed for brimonidine tartrate by film hydration technique and dispersed in viscous carbopol solution had the potential in reducing dosing frequency and could improve patient compliance [4]. Surface-modified SLNs containing timolol with phospholipid formulated by melt emulsification with high-pressure homogenization, could provide an efficient way of improving ocular bioavailability of timolol hydrogen maleate [17]. Acetzolamide-loaded cationic nanosized emulsion rather than anionic and neutral-charged emulsions could be suitable for eye drop in the treatment of glaucoma [18]. Seventeen dorzolamide hydrochloride nanoemulsions showed stable physicochemical properties and were nonirritant. The nanoemulsions can offer a intensive treatment of glaucoma [14].

Some Technique was Planned to Sustain the Operation Outcomes

LDL-mitomycin C-chitosan NPs can be applicable to anti-scarring therapy during excessive conjunctival wound healing [10].

CORNEAL DISEASES

NPs enhanced drug penetration [21]. The Cyclosporine A (CsA)-loaded or fluorescein-marked nanocarriers composed of Precipac ATO 5 and Miglyol 840 (as liquid lipid) were prepared by melting-emulsion technology. Lipid carriers (NLCs) was biocompatible and potential [22]. Indomethacin (IM)-Chitosan (CS)-nanoemulsion showed clearer healing of corneal chemical ulcer compared with NPs preparation and high level of IM in inner ocular structure thereby increasing drug delivery efficiency [23]. Positively charged fluorescent NPs by using the technique of non-invasive iontophoresis had showed better penetration abilities into inner ocular tissues [24]. CsA loaded SLN associated with CS were prepared by high shear homogenization and ultrasound method. CS-CsA-SLN were biocompatible and higher permeation in cornea and in RCE cell lines, pointing out the possibility of CsA targeting to the cornea [24-27]. SLN of baicalin was prepared by emulsification/ultrasonication method. This kind of NPs can retain better drug entity and ocular irritation. High concentration of baicain can be detected in aqueous humors [28]. Polymeric nanoparticle suspensions (NS) prepared by emulsion and solvent evaporation technique were loaded with diclofenac sodium (DS). NS showed a extended-release profile of DS and no irritant effect on cornea and iris thus can be suitable inert carrier for ophthalmic drug delivery [29]. Chitosan/thiolated chitosan-sodium alginate NPs (CS/THCS-SA NPs) could deliver greater amounts of drugs into HCE cells in vitro and cornea in vivo suggesting they have good potential for ocular drug delivery applications [30]. Poly (D, L-lactide-co-glycolide) withpoly (ethylene glycol) nanospheres (NSs) incorporating flurbiprofen (FB) penetrate corneal epithelium through transcellular pathway [31]. Gatifloxacin involved in polyglycidylated translocators nanodendrimers increased GFX solubility, rapid entrance into human corneal epithelial cells. Aqueous humor andivorous humor drug levels retained longer [32]. Fluorescent Hyaluronic acid-chitosan NPs prepared by ionotropigellation using fluoresceinamine-labeled
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hyaluronic acid and resuspended in buffer were compatible. Corneal tissue morphology and functionality did not show any changes[33]. Chitosan coated PLA Nano-carrier for topical ocular applications incorporated with 5-fluorouracil showed higher concentrations in aqueous and vitreous humor than free solution and better permeation efficiency for corneal[34].

**Keratoplasty** FK506 is an immunosuppressant. FK506 nanospheres prepared by using a biodegradable poly (lactic-co-glycolic acid) copolymer (PLGA) could suppress corneal graft rejection and prolong the allograft survival time[35].

**Corneal Neovascularization** Corneal neovascularization is a sight-threatening condition usually associated with disorders of the ocular surface. NPs delivering plasmids expressing Flt23k (an anti-VEGF intrareceptor) have a significant effect on decreasing corneal neovascularization and lymphangiogenesis, resulting in increased graft survival in penetrating keratoplasty[36]. The core/shell nanoparticle system with a photo-crosslinked shell layer by using a lecithin liposome as the core and pluronic F 127 diacrylate (DA-PF 127) as the shell layer increased structural stability of NPs. The core/shell nanoparticle loaded with VEGF resulted in more efficient in the therapy of new blood vessel formation[37]. Celastrol-loadedpoly (ethylene glycol) -block-poly (-caprolactone) nanopolymeric micelles was planned to improve the hydrophilicity of celastrol and significantly inhibited suture-induced corneal neovascularization[38].

**Viral Keratitis** SLNs and nanostructured lipid carriers (NLCs) were prepared by the modified hot oil in watermicroemulsion method, which have the potential to be developed further as ocular drug delivery systems for acyclovir[39].

**Wounds of the Corneal Epithelium** Inorganically-coated all-trans retinoic acid (atRA) NPs promotes wound healing and should be considered for the treatment of wounds of the corneal epithelium[40].

**Developments of NPs in the Therapy of Corneal Diseases**

**Corneal gene therapy** Gene therapy offers a promising alternative for the treatment of ocular diseases. Nanomedicine improves the transfection efficiency. Chitosan-DNA NPs has the proper nanoparticle size and positive zeta potential charge and can be pharmaceuticals for corneal gene therapy. Corneal fibroblasts can express the transgene green fluorescent protein [41]. Hybridizationated gelatin NPs which were developed by the ionic gelation technique contained polyanions (chondroitin sulfate dextran sulfate) can transfect ocular epithelial cells. NPs are effective vehicles for gene therapy and can increase the MUC5AC concentration in the ocular surface[42]. Oligodeoxynucleotides can be incorporated into poly (D,L-lactic-co-glycolic acid) NPs which were prepared by the method of double emulsion solvent evaporate and can transport into cells due to polymer erosion [43]. Hybrid NPs composed of cationizedgelatin and the polyanions CS and DS decreases the in vitro toxicity to corneal cells and let the NPs safer and more efficient [44, 45]. Nanoparticle made of two bioadhesive polysaccharides, hyaluronic acid (HA) and CS, deliver plasmid DNA to the cornea and conjunctiva[46]. 2-kDa polyethyleneimine conjugated to gold NPs (PEI2-GNPs) can get nitrogen-to-phosphorus ratios of up to 180 exhibited significant transgene delivery in the human cornea without any toxicity effect and can be uptaken through all the layers of cornea with gradual clearance[47]. Levofloxacin encapsulatedpoly (lactic-co-glycolic acid) NPs showed the nonirritant efficacy and longer retaining over precorneal area. The NPs can be measured of high entrapment efficiency and can be proved to be a stable formulation [48]. Self-assembled liquid crystalline NPs (cubosomes) for dexamethasone (DEX) increase the permeability and precocular retention. Good biocompatibility of DEX cubosomes were demonstrated by corneal cross-section[49].

**Corneal tissue engineering** SLNs incorporated with diclofenac sodium (DNA) were prepared with a combination of homolipid from goat and phospholipid. The permeation of DNA through the bio-engineered human cornea was improved [50]. Nanofibers prepared by industrial scale needleless technology were used as cell carriers for the regeneration of theinjured cornea. Nanofibrous materials can be tissue-engineered scaffolds for the corneal cells adhesion and mimic the native extracellular matrix[51].

**UVEITIS**

Autoimmune uveitis is an occcoectatio disease that targets the posterior part of the eye. More efficient modes of NPs drug delivery were applied in the treatments of immunological autoimmune uveitis with less side effects [52]. Nanocarriers permit the non-steroidal anti-inflammatory drug indomethacin to reach inner eye structures using the transmucosal route[53]. Intravitreal injection of dexamethasone (DEX)-loaded poly (lactic acid-co-glycolic acid) NPs can sustained DEX concentrations for a long time appearing in all the layers of the eye ball thus can be used for the treatments of posterior segment diseases [54]. The therapeutic effects of betamethasone phosphate (BP) encapsulated in biocompatible and biodegradable blended NPs of poly (lactic acid) (PLA) homopolymers and PEG-block-PLA copolymers (stealth nanosteroids) reduced the clinical scores of rats with experimental autoimmune uveoretinitis (EAU) and decreased the inflammatory cytokines in the retina of EAU by prolonged blood circulation [55]. NPs prepared by using sialyl-Lewis X conjugated liposome as a site-directed delivery system containing dexamethasone showed selective targeting to the autoimmune uveoretinitis[56]. Poly(lactic acid) NPs encapsulating BP was injected intravenously to EAU rats. Injected NPs remained for 7 days with reducing infiltration of activated T-cells and macrophages in addition
to the hypertrophy of Muller cells [56]. Polyethylene glycol (PEG)-coated NPs incorporated tamoxifen (NP-PEG-TAM) were injected into the vitreous cavity of rats with retinal soluble antigen (S-Ag)-induced EAU. Expressions of MHC class II (+) inflammatory cells, TNF-alpha, IL-1beta and RANTES mRNA decreased by the therapy [57]. NPs delivery system may lead to a new therapeutic strategy in controlling intraocular inflammation.

RETINAL DISEASES

The blood-retina barrier and sclera prevent high molecular weight drugs to reach the tight junctions in the retinal pigment epithelium with limited transcellular diffusion after systemic or topical application[69-69]. Intracellular drug delivery systems that achieve longer duration of pharmacological effect with lower administration frequency are urgently needed[69]. Intravitreal nanogold showed no signs of retinal or optic nerve toxicity during histologic examination by light microscopy[61]. Aerosolized NPs was used in the gas phase of vitrectomy performing antimetabolites for modulation of proliferative vitreoretinopathy, antimicrobial agents for endophthalmitis, antiangiogenic compounds for vasoproliferative disorders, corticosteroid delivery, and other pharmacotherapies directed at the retina and choroid [62]. Vacancy-engineered mixed-valence-state cerium oxide NPs (nanoceria particles) scavenge reactive oxygen intermediates as a direct therapy for multiple diseases suggests that they may represent a unique platform technology [69]. It is a very important application of NPs presented here and now a novel drug Ozurdex (dexamethasone intravitreal implant) had been under investigation in a clinical trial for the treatment of vitreoretinal disorders[62-66].

Retinal Gene Therapy

Subretinal injections of rhodamine labeled NPs using an RPE-specific reporter vector (VMD2-eGFP) can efficiently deliver genes to the RPE [67]. NPs can be prepared by interaction of cationic polymers with DNA, which facilitate uptake of plasmid DNA from digestion after systemic or topical application[68,69]. US and/or MBs could be used safely to enhance the delivery of NPs into RPE cells[69]. A novel synthetic peptide for ocular delivery was modified using poly (ethylene) glycol (PEG-POD) and used to compact DNA into NPs. The NPs was then injected to the subretinal space with no toxicity and can protect plasmid DNA from digestion [70]. After the subretinal injection of goat IgG-adsorbed GNPs, GNPs located in the outer segments and in the lysosomes in the RPE without cytotoxicity. Goat IgG was successfully delivered in photoreceptor cells and RPE using GNPs. This might be an alternative drug delivery method to photoreceptors and RPE [71]. The human serum albumin NP developed by a desolvation-crosslinking method offers a very promising approach for nonviral gene delivery to the retina[72]. SLNs revealed a delay in cell uptake of the vectors in ARPE-19 cells, this cell line hampers the entrance of DNA into the nucleus [73]. Compacted DNA NPs treatment strategy appears to be clinically viable and provides a highly efficient non-viral technology to safely deliver and express nucleic acids in the retina and other ocular tissues[74].

Age–Related Macular Degeneration

PEGylated liposome-protamine-hyaluronic acid NPs (PEG-LPH-NP) loaded with siRNA (PEG-LPH-NP-S) will be promising for the treatment of choroidal neovascularization [75]. Cerium oxide NPs intravitreal injection inhibit: the reactive oxygen species rise and the formation of intraretinal and subretinal neovascular lesions. This character will be potential for treatment of neurodegenerative diseases such as age-related macular degeneration (AMD) and diabetic retinopathy [76]. Cerium oxide NPs, which had neuroprotective catalytic activities was potential for the treatment of inherited retinal degeneration[77]. Nanoparticle-mediated delivery of plasmogen kringle 5 (K5) reduced vascular permeability and the expressions of VEGF, TNF-α, ICAM-1, β-catenin, MCP-1 and TNF-α.K5 mediates a sustained inhibitory effect on choroidal neovascularization and thus has therapeutic potential for AMD and diabetic retinopathy[75-79]. Gold nanoparticle (GNP) could inhibit retinal neovascularization by intravitreal injection. GNP inhibit VEGF induced retinal microvascular endothelial cells proliferation and new vessel formation[75-79]. SLNs may facilitate continuous, noninvasive treatment of patients with retinitis pigmentosa and other retinal pathologies, increased photoreceptor survival, preserved photoreceptor morphology, and extended the ability of the retina to respond to light as assessed by electrotoretinography[80]. Microneedles can be a potent technique to deliver nanoparticle to the posterior eye[81]. 20nm gold NPs could be an alternative for drug delivery across the blood-retinal barrier (BRB), distributed in all retinal layers [80]. Polyactic acid/polyactic acid-polyethylene oxide NPs (PLA/PLA-PEO) encapsulating the water-soluble integrin-antagonist peptide, C16Y (C16Y-NP).

Choroidal Neovascularization

Choroidal neovascularization originated from AMD was smaller by injection of NPs of biodegradable polymers without toxicity effects [80]. Intravitreal injection of basic fibroblast growth factor-impregnated NPs (bFGF-NPs) prevent photoreceptor degeneration by inhibiting apoptosis in rat retina [82]. Subretinal delivery of polyethylene glycol-substituted lysine peptide (CK30PEG)-compacted DNA NPs results in efficient gene expression in retinal cells. Inflammatory cytokines monocyte chemotactic protein-1, chemokine KC, macrophage marker F4/80 or myeloid marker myeloperoxidase showed at control levels post injection [83]. NPs intravitreal injection was appropriate for the treatments of retinal diseases.

Poisonous Effect on Retina

The water-soluble nanoparticle hydroxylated fullerene [fullerol, nano-C60(OH)(22-26)] was cytotoxic toward hRPE cells and retinal damage maintained
in concentration higher than 10 mmol/L. Anti-angiogenic potential of silver NPs, produced by Bacillus licheniformis inhibit Bovine retinal endothelial cells survival by enhancement in caspase-3 activity and DNA ladders formation. Magnetite NPs coated with triblock copolymers containing polyethyleneoxide tail lengths of above 2kDa are biocompatible and appropriate for in vivo application. The NPs with polyethyleneoxide less than that will be toxic. Implications or safety issue are always a big issue for therapeutic application of "foreigners" in eye and other organs. The application of the structure-toxicity paradigm to nanomaterials represents a promising approach to decrease its side effects. The future possibilities of nanoparticles as drug delivery systems will be hypotoxic.

**CHALLENGES OF NPs**

In this review, we introduce the NPs applications in different eye diseases. Although nanoparticulate drug delivery was one of the most promising technologies to overcome poor stability in physiological medium and delivering them across biological barriers. NPs as drug or gene carriers had no influence on cornea, iris and even retina. Analysis for evaluation of the biological effects needs further observations. Nanomedicine gain Gold NPs requires heating and long incubation times are needed. NPs incorporation of high amounts of DNA will be challenges for gene delivery. The surfaces of insoluble particles and factors released by soluble NPs will interact with biological systems. Rational design of nanomaterials needs to be modified. Future work should focus on trialing combinations of additives to enhance favourable properties. Clinical development is ongoing and it will be interesting what benefits can these innovative drugs provide for patients.

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